PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JH/ml000065wo		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/01368	18/02/2000	19/02/1999
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant OCTAGENE GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/09/2000	25.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Surdej, P Telephone No. +49 89 2399 7334

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/01368

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-46	as originally filed			

Claims, No.:

1-49	as received on	26/05/2001	with letter of	25/05/2001

Drawings, sheets:

1-21	as originally filed

Sequence listing part of the description, pages:

1-20, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☒ contained in the international application in written form.
   - ☒ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 28-33.

because:

   ☒ the said international application, or the said claims Nos. 28-33 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-33.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15,18-20,22-33
	No:	Claims	16-17,21
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	1-27
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

D1: WO 94 28150 A (UNIV MCGILL) 8 December 1994 (1994-12-08)

D2: V. BOONYARATANAKORNKIT ET AL.: 'High-mobility group chromatin proteins 1 and 2 functionally interact with steroid hormone receptors to enhance their DNA binding in vitro and transcriptional activity in mamalian cells' MOL. CELL. BIOL., vol. 18, no. 8, August 1998 (1998-08), pages 4471-4487, cited in the application

D3: WO 94 17182 A (RES INST OF THE PALO ALTO MEDI ;LEAVITT JOHN C (US)) 4 August 1994 (1994-08-04)

D4: WO 93 20218 A (CONNAUGHT LAB ;FILMUS JORGE (CA); KLEIN MICHEL (CA)) 14 October 1993 (1993-10-14)

D5: WO 94 29471 A (GENETIC THERAPY INC) 22 December 1994 (1994-12-22)

D6: WO 93 23431 A (BAYLOR COLLEGE MEDICINE) 25 November 1993 (1993-11-25) cited in the application

D7: CROSSLEY M. ET AL: 'Recovery from hemophilia B Leyden: An androgen-responsive element in the factor IX promoter.' SCIENCE, (1992) 257/5068 (377-379)

D8: NORDEEN S.K. ET AL: 'Extreme position dependence of a canonical hormone response element.' MOL. ENDOCRINOL. 1998, vol. 12, no. 6, pages 891-898

Document D8 is known to the Applicant.

Introduction

The application discloses: A nucleic acid construct comprising at least one hormone responsive element (HRE) and a transgene wherein said HRE is not functionally linked to the transgene and uses of said construct, the use of (i) a nucleic acid acid construct comprising at least one HRE and a transgene, said at least HRE being not functionally linked to the transgene and (ii) a hormone-hormone receptor complex for preparing an agent for gene transfer, the use of a nucleic acid construct comprising at least one HRE and a transgene for preparing an agent for gene transfer.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The amendments filed with the letter dated 25 May 2001 appear to be acceptable under Article 34(2)(b) PCT. Therefore, the International Preliminary Examination Report (IPER) is established taking into account the amended set of claims.

2. **Claims 28-33** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

Lack of unity of invention

3. In response to the invitation mailed on 14 November 2000, the applicant decided to pay additional fees for the groups of inventions 3 and 9 identified by the International Preliminary Examination Authority. Therefore, the first opinion was established on the groups of inventions 2, 3 and 9. The reasoning containing the considerations behind the finding of lack of unity on the set of claims considered for said invitation is presented below in order to give the reasons for establishing the IPER only on claims 1-33 (see point 8).

4. **11** separate groups of inventions are identified:

1. Claims 1-12 and 29-31 (all partially): Use of a nucleic acid construct comprising at least one HRE **functionally linked** to a transgene, wherein the transgene is neither factor VIII, nor factor IX, nor von Willebrand factor, for preparing an agent for gene transfer. Method for gene transfer which comprises administering said agent to an organism or cellular system.
2. Claims 1-12 and 29-31 (all partially): Use as 1, except that the transgene is factor VIII.
3. Claims 1-12 and 29-31 (all partially): Use as 1, except that the transgene is factor IX.

4. Claims 1-12 and 29-31 (all partially): Use as 1, except that the transgene is von Willebrand factor.

5. Claims 13-16 and 29-31 (all partially): Use as 1, wherein the agent further comprised a hormone-hormone receptor complex and wherein the transgene is neither factor VIII, nor factor IX, nor von Willebrand factor.

6. Claims 13-16 and 29-31 (all partially): Use as 5, except that the transgene is factor VIII.

7. Claims 13-16 and 29-31 (all partially): Use as 5, except that the transgene is factor IX.

8. Claims 13-16 and 29-31 (all partially): Use as 5, except that the transgene is von Willebrand factor.

9. Claims 1-16, 29-31 (partially), 17-28, 32-34 (completely): A nucleic acid construct with at least one HRE which is **not functionally linked** to the transgene and its uses.

10. Claims 35-37: Use of a steroid hormone for preparing an agent for gene transfer.

11. Claim 38: Method for gene transfer which comprises administering a nucleic acid construct to an organism or to a cellular system, wherein the nucleic acid construct contains a transgene and is encapsulated in a steroid hormone.

5. D1-D6 disclose a nucleic acid construct comprising at least one hormone responsive element (HRE) and a transgene for preparing an agent for gene transfer and its uses. D1, D2, D4 and D6 disclose nucleic acid constructs which have a promoter consisting of at least one glucocorticoid response element (which is reponsive to progesterone) linked e.g. to a CAT reporter gene and such said constructs are transfected into cells (D1: e.g. abstract, page 10, 3rd paragraph; D2: e.g. page 4474, left column, 4th paragraph to right column, first paragraph; D4: e.g. abstract, page 7, 4th paragraph; D6: e.g. page 21, example 2 and page 24). D3 discloses promoter-carrying constructs which are inducible by progesterone in hormone responsive cells and which are linked e.g. to CAT (e.g. abstract). D5 discloses nucleic acid constructs which have a promoter consisting of at least one glucocorticoid response element (e.g. from mouse mammary tumor virus/long terminal repeat promoter) linked e.g. to factor VIII or IX genes and such said constructs are transfected into cells (e.g. abstract, pages 10 and 16).

6. The only common technical features which can be distinguished between: **1.** independent claims (1 and 17) and 38 is **a nucleic acid construct comprising a transgene, 2.** claim 35 and the other independent claims is **an agent for gene transfer, 3.** independent claims 1 and 17 are **a nucleic acid contruct comprising at least one HRE and a transgene, 4.** the subject matters of claim 5 is **a nucleic acid construct containing a HRE linked to a blood clotting factor gene**.

7. Since the said common technical features mentioned in point 6 are known from the prior art documents D1-D6 (see point 5), the subject matters of claims 1, 5, 13, 17, 35 and 38 are not so linked as to form a single general inventive concept (Rule 13.1 PCT) as they appear not to be linked by a new and inventive common special technical feature in the sense of Rule 13.2 PCT by taking into account the state of the art.

8. In response to the first opinion, the Applicant filed an amended set of claims corresponding to group 9 of inventions as well as groups 5-8 of inventions: Group 9 of invention corresponds to claims 1-33 and groups 5-8 of inventions correspond to claims 34-49. **Since no additional fees were paid to examine the subject-matter of claims 34-49, the IPER is established only on the subject-matter of claims 1-33.**

9. Further detailed analysis of group 9 of inventions examined in this opinion reveals an additional lack of unity. The only common technical features between claims 1 and 22 is **a nucleic acid construct comprising at least one hormone responsive element not functionally linked to a transgene**. D8 discloses said technical features (e.g. abstract). Therefore, claims 1 and 22 are not so linked as to form a single general inventive concept (Rule 13.1 PCT) as they appear not to be linked by a new and inventive common special technical feature in the sense of Rule 13.2 PCT by taking into account the state of the art. Hence, claims 1-21 and 28-33, on one hand, and 22-27, on the other hand, represent two separate groups of inventions.

Re Item V

Reasoned statement under Article 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty and inventive step (Art. 33(1)-(3) PCT)

Invention 9 - Claims 1-33 (completely): A nucleic acid construct with at least one HRE which is **not functionally** linked to the transgene and its uses.

10. **Claims 16-17 and 21** are not new. D8 discloses a nucleic acid construct comprising one or several hormone responsive elements (progesterone/ glucocorticoid receptor-binding site) not functionally linked to a transgene which is the gene for chloramphenicol acetyltransferase (e.g. abstract, fig. 2, fig. 5, page 894, left column, last paragraph, page 895, left column, last paragraph). For example, no or little expression of the transgene is detected when constructs have the HRE located between positions 50 and 100 and after position 100 (Fig. 2), consequently no functional link between the HRE and the transgene is present for said constructs. In addition, the composition disclosed in D8 comprises a nucleic acid construct comprising one (or several) HRE and a transgene, said HRE is coupled to hormone-hormone receptor complex (whether the HRE is functionally linked to the transgene or not) when said construct is transfected into progesterone receptor-expressing fibroblastes or a human carcinoma cell line expressing both glucocorticoid and progestin receptor.

11. **Claims 18-20 and 22-27** are new but not inventive in the light of D5, D7 and D8. The features referred to in said claims merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.

12. An inventive step cannot be acknowleged from **claims 1-15 and 29-33** since the problems of the said claims appear not to be solved.
The technical problem of claims 1-15 is defined as an alternative method of preparing an agent for gene transfer.
The technical problem of claim 29-33 is defined as an alternative way for

delivering into an organism or into a cellular system a nucleic acid encoding a transgene to be expressed in the cells of the organism or the cells of the cellular system.
No solution to said technical problems is provided in the application for the following reasons:

The only possible example which might support said subject-matter is example 9 together with Figs. 17 and 18. In example 9, the human progesterone receptor, a micronized progesterone and a plasmid carrying human factor IX are used for oral gene transfer in mouse.

Fig. 17 shows an overlap between the standard deviation values of all groups 1-4 (control samples) and group 5 (test sample). Moreover, the mean value of the test sample falls into the standard deviation values of group 2 and 4. Consequently, the person skilled in the art is not in the position to differentiate the invention from the prior art.
In addition, it is not clear from the example whether the plasmid comprises at least one hormone responsive element which is **not functionally linked** to the transgene.
Even if said example might provide a support to the claimed subject-matter, it would be only for a hormone-hormone receptor complex consisting of progesterone receptor and progesterone and a progesterone responsive element since hormone-hormone receptor complexes in general vary greatly in their properties and the specific example disclosed in the application is not a sufficient basis to support a broad claim such as claim 1, for example.
Since no effect is seen over the prior art, the requirement of Art. 33(3) PCT is not fulfilled.
Furthermore, the subject-matter of said claims is not sufficiently disclosed (Art. 5 PCT).

Article 5 PCT requires an invention to be disclosed in a manner sufficiently clear and complete to be carried out by a person skilled in the art. This means that the skilled person should be able, after reading the description, to performe the invention over the whole range claimed without undue burden and without an inventive step. The extent to which an invention is sufficiently disclosed is relevant

when considering the issue of support in the sense of Articles 5, 6 and 33 (2)-(4) PCT.

Industrial Applicability (Art. 33. (1) and (4) PCT)

13. For the assessment of the present **claims 28-33** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

14. The expressions following the term "preferably", e.g. in claims 5-7 are regarded as having no limiting effect on the scope of the said claims and are therefore not taken into account for the opinion on said claims (the PCT Preliminary Examination Guidelines Ch. III-4.6).

PCT/EP00/01368 JH/ml

Octagene GmbH May 25, 2001

CLAIMS

1. Use of
(i) a nucleic acid construct comprising at least one hormone responsive element (HRE) and a transgene, said at least one HRE being not functionally linked to the transgene, and
(ii) a hormone-hormone receptor complex
for preparing an agent for gene transfer.

2. The use of claim 1, wherein the transgene is selected from the group consisting of genes encoding a blood clotting factor, hormone genes, hormone receptor genes, growth factors, enzyme genes, genes encoding cytokines or lymphokines, genes encoding inhibitor substances, genes encoding substances that function as drugs or vaccines, and antisense sequences.

3. The use of claim 2, wherein the transgene is a gene encoding a blood clotting factor and the agent is suitable for treating hemophilia.

4. The of claim 3, wherein the blood clotting factor is a human blood clotting factor and preferably is selected from the group consisting of factor VIII, factor IX, and von Willebrand Factor (vWF).

5. The use of any one of claims 1 to 4, wherein the nucleic acid construct comprises 1 to 20, preferably 3 to 10 HRE(s).

6. The use of any one of claims 1 to 5, wherein the at least one HRE is a steroid responsive element, preferably a progesterone responsive element (PRE).

7. The use of claim 4, wherein the HRE is a PRE and the blood clotting factor is factor IX, preferably the factor IX has a nucleotide sequence of 689 to 2071 of SEQ ID NO: 1.

8. The use of claim 5, wherein the HRE is a PRE and the blood clotting factor is factor VIII.

9. The use of any one of claims 6 to 8, wherein the PRE has the double stranded DNA sequence comprised of the DNA sequences of SEQ ID NOs: 3 and 4.

10. The use of any one of claims 1 to 9, wherein the construct further comprises functional DNA sequences selected from the group consisting of promoter sequences, enhancer sequences, silencer sequences, origin of replication sequences, integrational sequences, marker genes and switch sequences.

11. The use of claim 10, wherein the construct further comprises a tissue-specific promoter, preferably an α-antitrypsin promoter.

12. The use according to any one of claims 1 to 11, wherein the hormone-hormone receptor complex is a steroid-steroid receptor complex.

13. The use of claim 12, wherein the molar ratio of HRE within the nucleic acid construct to hormone receptor is from 1:1 to 1:10, preferably 1:2 to 1:5, and/or the molar ratio of hormone to hormone receptor is at least 1000:1, preferably at least 10000:1.

14. The use of claim 12 or 13, wherein the receptor is a progesterone receptor and the steroid is progesterone or a progesterone derivative.

15. The use of claim 14, wherein the progesterone is natural micronized progesterone solubilized in a liphophilic matrix system and/or the progesterone receptor is hPR-A, hPR-B or comprises the nucleotide sequence of 557 to 933 SEQ ID NO:18.

16. A pharmaceutical composition comprising a nucleic acid construct comprising at least one HRE and a transgene as defined in claims 1 to 11 and/or a vector comprising said nucleic acid construct, said at least one HRE being coupled to a hormone-hormone receptor complex.

17. The pharmaceutical composition of claim 16, wherein the hormone-hormone receptor complex is as defined in claims 12 to 15.

18. The pharmaceutical composition of claim 16, wherein the transgene is a gene encoding a blood clotting factor.

19. The pharmaceutical composition of claim 18 wherein the blood clotting factor is factor IX.

20. The pharmaceutical composition of claim 18 wherein the blood clotting factor is factor VIII.

21. The pharmaceutical composition of any one of claims 18 to 20, which is suitable for gene transfer, preferably for treating hemophilia.

22. A nucleic acid construct comprising at least one HRE and a transgene being a gene encoding a blood clotting factor, wherein one of said at least one HREs is not functionally linked to the transgene.

23. The nucleic acid construct of claim 22, which is as defined in claims 4 to 11.

24. A vector comprising the nucleic acid construct of claim 22 or 23.

25. A transformed cell or transgenic organism comprising the nucleic acid construct as defined in claims 22 or 23 or the vector as defined in claim 24.

26. A composition of matter comprising
- the nucleic acid construct comprising at least one HRE and a transgene as defined in of claim 22 or 23, and/or
- a vector comprising said nucleic acid construct, said at least one HRE being coupled to a hormone-hormone receptor complex.

27. A method for preparing the composition of matter as defined in claim 26, which method comprises admixing the nucleic acid construct with the hormone receptor and the hormone.

28. A method for gene transfer which comprises administering the agent as defined in claims 1 to 15, or the pharmaceutical composition as defined in claims 16 to 20 to an organism or to a cellular system.

29. A method for delivering into an organism or into a cellular system a nucleic acid encoding a transgene to be expressed in the cells of the organism or the cells of the cellular system, which method comprises administering an agent as defined in claims 1 to 15 or a pharmaceutical composition as defined in claims 16 to 20 to the organism or to the cellular system so that the hormone in the composition interacts with the cell membrane and therewith enhances diffusion and transport of the nucleic acid that is coupled to the hormone-hormone receptor complex across the membrane and into the cell.

30. The method of claim 29, wherein a nucleic acid encoding human factor VIII or factor IX is delivered into the cell.

31. A method of treating blood clotting disorders comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 18 to an organism or to a cellular system.

32. A method of treating hemophilia B, comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 19 to an organism or to a cellular system.

33. A method of treating hemophilia A, comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 20 to an organism or to a cellular system.

34. Use of
(i) a nucleic acid construct comprising at least one hormone responsive element (HRE) and a transgene wherein the transgene is a gene encoding a blood clotting factor and the at least one HRE is functionally linked to the transgene, and
(ii) a hormone-hormone receptor complex
for preparing an agent for treating heomphilia.

35. The of claim 34, wherein the blood clotting factor is a human blood clotting factor and preferably is selected from the group consisting of factor VIII, factor IX, and von Willebrand Factor (vWF).

36. The use of claims 34 or 35, wherein the nucleic acid construct comprises 1 to 20, preferably 3 to 10 HRE(s).

37. The use of claim 34 to 36, wherein the at least one HRE is a steroid responsive element, preferably a progesterone responsive element (PRE).

38. The use of claim 35, wherein the HRE is a PRE and the blood clotting factor is factor IX, preferably the factor IX has a nucleotide sequence of 689 to 2071 of SEQ ID NO: 1.

39. The use of claim 35, wherein the HRE is a PRE and the blood clotting factor is factor VIII.

40. The use of claim 37 to 39, wherein the PRE has the double stranded DNA sequence comprised of the DNA sequences of SEQ ID NOs: 3 and 4.

41. The use of claims 34 to 40, wherein the construct further comprises functional DNA sequences selected from the group consisting of promoter sequences, enhancer sequences, silencer sequences, origin of replication sequences, integrational sequences, marker genes and switch sequences.

42. The use of claim 41, wherein the construct further comprises a tissue-specific promoter, preferably an α-antitrypsin promoter.

43. The use according to any one of claims 34 to 42, wherein the hormone-hormone receptor is a steroid-steroid receptor complex.

44. The use of claim 43, wherein the molar ratio of HRE within the nucleic acid construct to hormone receptor is from 1:1 to 1:10, preferably 1:2 to 1:5, and/or the molar ratio of hormone to hormone receptor is at least 1000:1, preferably at least 10000:1.

45. The use of claim 43 or 44, wherein the receptor is a progesterone receptor and the steroid is progesterone or a progesterone derivative.

46. The use of claim 45, wherein the progesterone is natural micronized progesterone solubilized in a liphophilic matrix system and/or the

progesterone receptor is hPR-A, hPR-B or comprises the nucleotide sequence of 557 to 933 SEQ ID NO:18.

47. A method for gene transfer which comprises administering the agent as defined in claims 34 to 46 to an organism or to a cellular system.

48. A method for delivering into an organism or into a cellular system a nucleic acid encoding a transgene to be expressed in the cells of the organism or the cells of the cellular system, which method comprises administering an agent as defined in claims 34 to 46 to the organism or to the cellular system so that the hormone in the composition interacts with the cell membrane and therewith enhances diffusion and transport of the nucleic acid that is coupled to the hormone-hormone receptor complex across the membrane and into the cell.

49. The method of claim 48, wherein a nucleic acid encoding human factor VIII or factor IX is delivered into the cell.